Müllerian Duct Anomalies: Clinical Issues and of 3D Ultrasound Diagnosis

Mihaela Grigore, MD, PhD[1], Camelia Cojocaru, MD[2], Alina Mareș, MD[3], Anca Indrei, MD, PhD[4]

1. Department of Obstetrics and Gynecolgy, University of Medicine and Pharmacy Gr.T. Popa Iasi, Medis Medical Center; 2. Cuza Vodă Hospital Iași, Medis Medical Center Iasi; 3. Cuza Vodă Hospital Iași; 4. Deparment of Anatomy, University of Medicine and Pharmacy Gr.T. Popa Iași

Correspondence:
Mihaela Grigore
e-mail: mihaela.grigore@edr.ro

Abstract

The incidence of uterine malformations is estimated to be between 3% and 4% in the general population. Their impact is noted in infertility problems such as preterm labor, intrauterine growth restriction and pathological lie or presentation. Until recently, the use of invasive tests, such as laparoscopy, hysteroscopy, or hysterosalpingography, was required for diagnosing congenital uterine anomalies. Since some of this malformation can be surgically corrected, pre-surgical pelvic imaging has both a diagnostic and a therapeutic value.
One of the common imaging methods is the pelvic sonogram. A major disadvantage of two-dimensional pelvic sonogram is its inability to reconstruct the uterine coronal axis. The imaging of this axis has major significance in diagnosing the uterine fundus malformation. In recent years further advances in ultrasonography have led to three-dimensional ultrasonography (3DUS).
This review shows the advantages of the three-dimensional ultrasound as a diagnostic tool. The authors also present several examples of uterine malformations from their own experience.
Keywords: *uterine malformations, clinical issues, 3D ultrasound*

The incidence of uterine malformations is estimated to be between 3% and 4% in the general population. The prevalence of the particular types of the uterine malformations is difficult to assess due to the different populations studied, to small sample sizes, to prospective versus retrospective study designs, to different classification systems, and to the types of test used in diagnosing[(1)].

Embryology

The uterus develops from the two paramesonephric ducts (Mullerian ducts). The caudal two thirds of these ducts give rise to the uterus and the upper third become the Fallopian tubes. The development of the uterus is divided into the three stages and failure or arrest of development during these stages explains the occurrence of uterine malformations.

There are four other important facts to be kept in mind:

- uterine malformations are often associated with upper vaginal malformations because the 2/3 of the vagina has the same embryologic origin as the uterus
- uterine anomalies are often associated with urinary tract anomalies (kidneys, urethra) due to close embryological interactions;

Table 1

The development of the uterus and uterine malformations

Stage	Normal development	Failure of normal development	Uterine malformations
6-9 weeks	■ The appearance of Müllerian ducts and their caudal midline fusion and connection with urogenital sinus	→	Uterine aplasia
10-13 weeks	■ The upward fusion of the caudal parts of the Müllerian ducts	→	Uterine duplications- uterus didelphys, bicornuate uterus
4-18 weeks	■ The resorption of the medial septum initially separating the caudal parts of the Müllerian ducts to form the uterovaginal duct as the origin of both uterine cavity and superior 2/3 of the vagina	→	uterine septation (septate uterus)

- the independent ovarian and Müllerian ducts development explains the generally normal ovarian morphology and function in the cases of uterovaginal developmental anomalies;
- uterine malformations are usually not associated with chromosomal or sexual differentiation anomalies.

Classification

The most basic classification of Müllerian duct defects consists of agenesis and hypoplasia, defects of vertical fusion, and defects of lateral fusion. In 1979, Buttram and Gibbons proposed a classification of Müllerian duct anomalies that was based on the degree of failure of normal development, and they separated these anomalies into classes that demonstrate similar clinical manifestations, treatment, and prognosis for fetal rescue[2]. This classification was modified in 1988 by the American Fertility Society (now the American Society of Reproductive Medicine), and at the moment this represent the most used one[3]. The American Fertility Society (AFS) classified Müllerian anomalies according to the major uterine anatomic types:

1. Hypoplasia/agenesis - segmental agenesis and variable degrees of uterovaginal hypoplasia;

2. Unicornuate uterus - partial or complete unilateral;

3. Didelphys uterus - duplication of the uterus results from complete nonfusion of the Müllerian ducts;

4. Bicornuate uterus - demonstrates incomplete fusion of the superior segments of the uterovaginal canal;

5. Septate uterus - represent partial or complete nonresorption of the uterovaginal septum;

6. Arcuate uterus - result from near complete resorption of the septum;

7. DES drug related uterus - comprises sequelae of in utero DES exposure.

As observed, this classification has simplified the categorization of Müllerian anomalies. However, some uterine anomalies may have characteristics of one or more categories. Despite its flaws, the AFS classification provides a basis for communication and comparison between investigators.

Septate Uterus

The septate uterus is the most common Müllerian duct anomaly. Fifty-five percent of uterine anomalies are septate[4,5]. This anomaly results from partial or complete failure of resorption of the uterovaginal septum after fusion of the paramesonephric ducts. Since the paramesonephric ducts have previously fused, the serosa of the uterine fundus is intact. The septum arises in the midline fundus and can be complete or partial. A complete septum extends to the external cervical os[6]. A partial septum is variable in length and may be mild or extend to the endocervical canal proximal to the external os. The external uterine contour may be convex, flat, or mildly concave[4,7]. Although the AFS classification do not specify the minimal depth of fundic indentation for differentiation of a septate from a bicornuate or a uterus didelphys the general consensus is that a distance of less than 1 cm will differentiate between the septate uterus and bicorn uterus[4]. When the serosal indentation is more than 1 cm, this indicates a bicornuate uterus[8]. The configuration of the external uterine contour is essential for the differentiation of a septate from a bicornuate uterus, because different clinical and therapeutic approaches are assigned to each anomaly[9]. The surgical treatment for a septate uterus is hysteroscopic resection of the septum. Bicornuate uteri rarely necessitate surgical intervention, although Strassman metroplasty (wedge resection of the medial aspect of each uterine horn and subsequent unification of the two cavities) may be applied in patients with recurrent second-trimester abortion and premature delivery[10]. It is important to recognize that mild concavity of the external uterine contour should not be construed as a "partial" bicornuate configuration, because these patients may not be given the option of hysteroscopic metroplasty.

In general, septate uteri have the poorest reproductive outcomes of Müllerian anomalies[6]. The poor reproductive outcome can be explained by several mechanisms:

- endometrial mucosa covering the septum does not respond appropriately to estrogen
- abnormal distribution of vessels within the septum
- irregular contractions of muscular fibers in the septum[8,11,12,13].

Salim et al have reported that the more complete the septum, the higher the pregnancy failure rate[12]. It has not yet been determined why some patients with a septate uterus carry a pregnancy to term and others have

recurrent miscarriages[11]. Because it is not always associated with a poor obstetrical history, the incidental finding of a uterine septum is not an indication for hysteroscope incision[4,11]. Hysteroscopic incision of a septum (in order to restore normal uterine cavity) is indicated in women with a longstanding history of unexplained infertility. When evaluating the uterus following hysteroscopic metroplasty, no residual septum or evidence of a residual septum measuring up to 1 cm in length is considered indicative of optimal resection[14]. Reproductive outcome has been shown to improve after resection of the septum, with reported decreases in the spontaneous abortion rate from 88% to 5.9% after hysteroscopic metroplasty[4, 14,15,16].

Arcuate Uterus

An arcuate uterus has a broad indentation of the fundal endometrium. The indentation of the endometrium at the uterine fundus is a result of near complete resorption of the uterovaginal septum. It remains controversial as to whether an arcuate uterus is a normal variant or a true muellerian anomaly[5]. In the original Buttram and Gibbons classification, the arcuate uterus was subclassified with the bicornuate uterus because it "most closely resembles a 'mild' form of bicornuate uterus"[2]. The AFS designated a separate class for this anomaly, because the arcuate uterus can be distinguished from a bicornuate uterus on the basis of its complete fundic unification. The depth of the indentation that would distinguish and arcuate from a small partial septum is not yet well defined[8]. As result, it is not surprising that both poor and good obstetric outcomes have been reported in patients with an arcuate shaped uterus[17]. Data regarding the reproductive outcomes of patients with an arcuate uterus are extremely limited and contradictory. Both poor and good obstetric outcomes have been reported, although an arcuate configuration is generally thought to be compatible with normal-term gestation, with a quoted delivery rate of 85%[11]. Hysteroscope incision has been performed in patients with an arcuate shaped uterus and recurrent pregnancy loss[8]. It has been proposed that when a ratio of less than 10% between the height of the fundic indentation and the distance between the lateral apices of the horns is calculated on the basis of HSG findings, an adverse reproductive outcome is not anticipated[4]. However, a defining depth of the indentation to differentiate an arcuate configuration from a broad septum has not been established.

Bicornuate Uterus

Ten percent of uterine anomalies are bicornuate which results from incomplete fusion of the uterine horns. A bicornuate uterus consists of two symmetric cornua with communication of the endometrial cavities most often at the level of the uterine isthmus.. The intervening myometrium extends for a variable length from the fundus to the cervix. A complete bicornuate uterus may have a single (bicornuate unicollis) or duplicated (bicornuate bicollis) cervix. The incidence of spontaneous abortion is 28-35% and of the premature delivery birth range from 14% to 23%[6]. Spontaneous abortion rates and preterm delivery are reported to be higher in women with a complete bicornuate uterus than in those with a partial bicornuate uterus[11].

It is important to differentiate between a partially septate and a partially bicornuate uterus. While hysteroscope resection is the treatment of choice for a sub-septate uterus, it is contraindicated for a bicornuate uterus[11]. Surgical intervention is usually not indicated, and the length of subsequent gestations often increases with increasing parity. Strassman metroplasty has been advocated in women with a history of recurrent pregnancy loss and in whom no other infertility issues have been identified[10]. However, the benefits of metroplasty have never been formally studied in a prospective trial[6]. Because the bicornuate uterus has been reported to have the highest associated prevalence (38%) of cervical incompetence among Müllerian duct anomalies, prophylactic placement of a cervical cerclage in selected patients has been reported to increase fetal survival rates[18].

Uterus Didelphys

Uterine didelphys represents 5% of Müllerian anomalies. This uterine anomaly is due to an almost complete failure of Müllerian duct fusion - there are two hemi-uteruses and two cervices. A longitudinal and transverse vaginal septum may also be present with subsequent hematometrocolpos. There is no communication between the duplicated endometrial cavities. Non-obstructive uterus didelphys is usually asymptomatic, while uterus didelphys with unilateral vaginal obstruction may become symptomatic at menarche and manifest as dysmenorrhea. Due to the retrograde menstrual flow in patients with obstruction, endometriosis and pelvic adhesions have an increased prevalence[19]. Spontaneous abortion rates are reported to range from 32% to 52%, premature birth rates range from 20% to 45% and fetal survival rates, from 41% to 64%[6]. Strassman metroplasty, leaving the duplicated cervix intact in an attempt to prevent cervical incompetence, is a consideration for selected patients with recurrent spontaneous abortions and premature deliveries[10]. As with the bicornuate uterus, however, the benefits of intervention remain unclear because no controlled trials have been performed[6].

Unicorn Uterus

Approximately 20% of uterine anomalies are unicornous. A unicorn uterus occurs when one Müllerian duct develops normally and the other does not - 1/3 are isolated, 1/3 have a non-cavity rudimentary horn and 1/3 have a cavity rudimentary horn that may or may not communicate with the unicornous cavity.

The obstetrical impact is represented by an increase incidence of spontaneous abortion (41-66%), premature birth (10-2-%), abnormal fetal lie, decrease fetal survival rates (38% to 57%) and intrauterine growth retardation[6,20]. The pathogenesis of pregnancy loss and decreased fetal survival rate of the unicorn uterus are incompletely understood. It has been hypothesized that inadequate vascularization and compromised uteroplacental blood flow of the unicorn uterus result from the decreased vascular contribution of the uterine and utero-ovarian arteries from the abnormal side[20].

Resection of a cavity rudimentary horn is recommended because of the substantial risk that a pregnancy in a non-communicating horn will rupture;

even in a communicating horn a viable pregnancy is rarely achieved(8). Surgical intervention in a rudimentary horn without associated endometrium is rarely indicated. Renal abnormalities are more commonly associated with unicorn uterus than with other Müllerian duct anomalies and have been reported in 40% of these patients[21]. The anomaly is always ipsilateral to the rudimentary horn. Renal agenesis is the most commonly reported abnormality, occurring in 67% of cases. Other renal anomalies which could be present are: ectopic kidney, horseshoe kidney, cystic renal dysplasia, and duplicated collecting systems.

DES-exposed Uterus

A T-shaped configuration of the endometrial cavity is the most commonly associated abnormality, seen in 31% of exposed women[22]. Other uterine corpus anomalies include a small hypoplastic uterus, constriction bands, a widened lower uterine segment, a narrowed fundic segment of the endometrial canal, irregular endometrial margins. Cervical anomalies occur in 44% of cases and include hypoplasia, anterior cervical ridge, cervical collar, and pseudopolyps. An abnormal cervical finding is associated with abnormal uterine corpus changes in 86% of cases. Exposed women are reported to be predisposed to cervical incompetence, secondary not only to structural changes but also to histological changes such as abnormal smooth muscle–to-collagen ratio and decreased cervical elastin[22].

Imaging of uterine malformations

Hysterosalpingography (HSG) provides a morphologic assessment of the endometrial and endocervical canals and supplies important information regarding tubal patency. The major limitations of the procedure are the inability to evaluate the external uterine contour adequately and exposure to ionizing radiation in young women. Characterization of uterine anomalies can be difficult, however, and there can be considerable overlap in findings, notably with regard to differentiation of a septate from a bicornuate uterus.

MRI has been the "gold standard" for categorizing uterine anomalies because of its very high accuracy (98%-100%). While ultrasound will remain the primary modality utilized to evaluate Müllerian anomalies, MRI can offer additional diagnostic information in patients with equivocal ultrasound findings. As a result, laparoscopy or open surgery is no longer required to make a definitive diagnosis of a uterine anomaly. However, access to this examination is still limiting factor in many countries.

Endovaginal ultrasound represents the main diagnostic method of uterine anomalies. The most precise investigation of uterine morphology can be done during the second half of menstrual cycle or at the beginning of pregnancy (the thick and echoic endometrium has a better contrast with the adjacent myometrium). The evaluation of the uterine malformations should be accompanied by the renal investigation in effort to find some associated anomalies. Although its clinical importance is well defined, 2D ultrasound has several limitations. For example unicorn uterus can be missed and discrete forms of septate and bicornuate uterus are not easy to distinguish among themselves. These inconveniences can be surpassed by 3D ultrasound. Woelfer, et al, have shown that three-dimensional ultrasound is accurate in depicting abnormal uterine shapes[23]. The process of 3D scanning consists of four basic steps: data acquisition, volume analysis and processing, image animation (cine loop), archiving the volumes. Once the volume has been stored, a single point in space can be selected in the volume, and this point can be visualized in all three perpendicular planes. The examiner can navigate through the volume, keeping track of a single point in space in all three planes. This is valuable not only for imaging the uterus and its adnexa, but also for measuring distances and even volumes of organs. It is possible to "rotate" the organ by spinning the image in any of the planes. Another advantage is navigation through a single plane while watching the corresponding effect on the other two planes. This gives us complete control of the volume to view it or perform measurements in any display desired. Advocates of three-dimensional ultrasonography suggest that these features offer the user the following advantages in comparison to two-dimensional ultrasonography:

- accurate measurement of organ dimensions and volumes,
- improved anatomic and blood flow information,
- improved assessment of complex anatomic anomalies,
- better specificity in regard to the confirmation of normality,
- standardization of the sonographic examination procedure,
- reduced scanning times with cost-effective use of equipment and sonographer time,
- possibility of post processing the volumes,
- telemedicine and tertiary consultation.

Uniquely, three-dimensional sonogram allows demonstration of the coronal plane perpendicular to the transducer face facilitating the identification of surface irregularities which can then be accounted for during volume measurement[24]. With 3D ultrasound it is easy to obtain the coronal view with the entire endometrial canal, the relationship of the endometrium to myometrium and the uterine serosa. It is best performed during the secretory phase of the menstrual cycle so the endometrial cavity is easier to outline. The three planes (longitudinal, sagittal, coronal) can be correlated by placing the image point or the intersection of the two perpendicular views at the region of interest. By scrolling the upper line of the field of view into the endometrial cavity, surface rendering of the serosa and endometrial cavity are visualized. Three-dimensional US with surface- and transparent-mode reconstructions of the uterus has reported advantages over conventional two-dimensional scanning. In experienced hands, a sensitivity of 93% and a specificity of 100% have been achieved[25].

In order to accurately measure the endometrial extension of a septum, a true coronal plane through the fundus and cervix must be obtained. If the plane is off center, an arcuate uterus may not be detected, the measurement of a septum will be inaccurate, and the detection of the serosa indentation of a bicornate uterus may be missed.

In a septate uterus 3 D ultrasound is

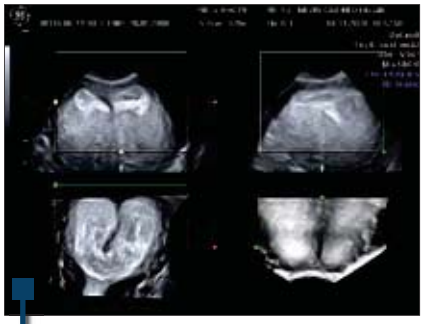

Figure 1. 3D ultrasound of septate uterus

Figure 2. 3D ultrasound of a septate uterus and pregnancy

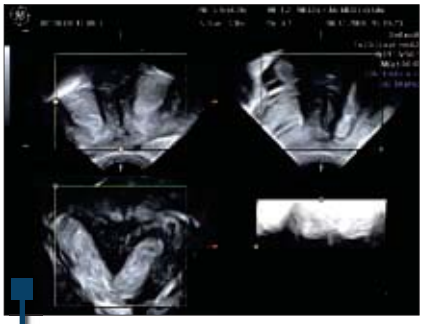

Figure 3. 3D ultrasound bicornuate uterus

Figure 4. Bicornuate uterus-coronal plane

Figure 5. Unicorn uterus-coronal plane

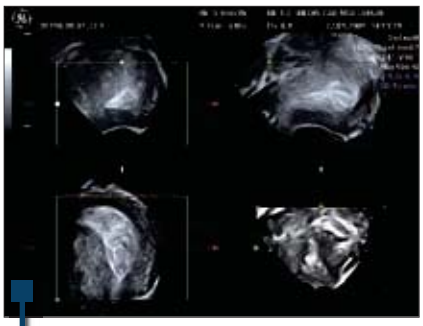

Figure 6. 3D ultrasound of unicorn uterus

used to evaluate the size and extent of septa (Figure 1 - 3D ultrasound of septate uterus). The sensitivity, specificity, positive and negative predictive values of 3D ultrasound in the detection of a septate uterus is 98.4%, 100.0%, 100.0% and 96.0%, respectively[25]. It is possible to confirm or exclude the diagnosis of a associated septated cervix. On coronal plane we can measure the distance between the two internal tubal ostia, the length of a septum, the remaining cavity length, and the depth of an external fundic indentation[23,26]. Quantification of these parameters provides a reproducible standard that can be used to compare studies from different institutions. It is useful for differentiation of septate from bicornuate uteri. Even so some difficulties could appear in diagnosis of a septate uterus with an external indentation. In this case the differential diagnosis with a bicornuate uterus could be difficult. On the cororнal plane obtained with 3D it is easy to measure the length of indentation; if it is less than 1 cm than the diagnosis is bicornuate uterus and if it is larger than 1 cm the diagnosis is bicornuate uterus. Also it is stated that an angle of less than 75° between the uterine horns is suggestive of a septate uterus, and an angle of more than 105° is more consistent with bicornuate uteri. Unfortunately, the majority of angles of divergence between the horns fall within this range, and considerable overlap between the two anomalies is noted. The coronal 3 D plane permit a very precise measurement of this angle[10]. US has been reported to allow differentiation of a septate from a bicornuate uterus if a true orthogonal view along the long axis can be obtained. In this plane, a line is drawn between the apices of the endometrium at the level of the ostia. If the fundic indentation of the external uterine contour is below the interostial line or less than 5 mm above the line, the uterus is considered to be bicornuate or didelphic. The septate uterus is defined by a fundic indentation of more than 5 mm above the interostial line[4]. Reconstruction of the coronal plane is also helpful in assessing gestational sac location within a bicornuate or septate uterus thus not mistaking a sac within a horn as a cornual pregnancy (Figure 2 - 3D ultrasound of a septate uterus and pregnancy).

In case of bicorn uterus on 3D ultrasound a large fundic cleft may be visualized (Figure 3 - 3D ultrasound bicornuate uterus). The depth of the cleft is > 1.0 cm. The horns of the endometrial cavity are usually widely separated with an intercornual angle greater than 105°. Each horn has a fusiform appearance, with apices that taper and end in a single fallopian tube (Figure 4 - Bicornuate uterus-coronal plane). As we have already stated the differentiation from the septate uterus is sometimes very difficult.

In case of a didelphic uterus on 3D ultrasound images, separate divergent uterine horns are identified, with a large fundic cleft. Endometrial cavities are uniformly separate, with no evidence of communication. Two separate cervices need to be documented. The distance between the uterine horns frequently prevents their visualization on a single 3D ultrasound image. The region of interest in the uterus must fit within the volume "box". The horns of a didelphic uterus are generally too far apart to be imaged with 3D ultrasound.

3D is extremely useful in diagnosing a unicorn uterus. The coronal

plane shows a spindle-shape elongated endometrial cavity and the characteristically asymmetric ellipsoidal shape of the uterus (Figure 5 - Unicorn uterus-coronal plane). These findings are very difficult to observe with 2D ultrasound and this explains why the unicorn uterus is often misdiagnose if only 2D is performed. The identification of a uterine cavity horn may be difficult to differentiate from other types of duplicated uterus. Three-dimensional US may help further characterize the anomaly (Figure 6 - 3D ultrasound of unicorn uterus). The 3D coronal plane shows the T-shape of the endometrial cavity and other minor findings consistent with DES-expose.

Conclusion

Uterine anomalies represent an important issue due to their high prevalence in general population and their impact infertility. The advent of three-dimensional (3D) ultrasound is one of the most important advances in gynecological ultrasound recently. The ability to view the uterus and endometrium in virtually any plane, has added greater diagnostic confidence to ultrasound imaging. While 2D transvaginal ultrasonography is an excellent screening examination for uterine anomalies, it is not as effective as 3D ultrasound in distinguishing specific malformations. 3D ultrasound does not replace 2D ultrasound but, rather, complements it. Uterine surgery to correct septum, for example, can be planned based on three-dimensional ultrasound imaging without the need for MRI, which until now was the only modality available to demonstrate uterine shape anomalies accurately.

Cut-off values for distinguishing arcuate, bicornuate, and septate uteri on 3D coronal images have, to date, been arbitrarily selected. By defining 3D diagnostic criteria, inter and intra-observer variability in detecting uterine malformations is quite good. The accumulation of data on specifically defined uterine anomalies will provide reliable incidence figures for uterine anomalies and outcome data that may result in anomaly-based management schemes. ■

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